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# Influence of mycotoxin binders on the oral bioavailability of doxycycline in pigs

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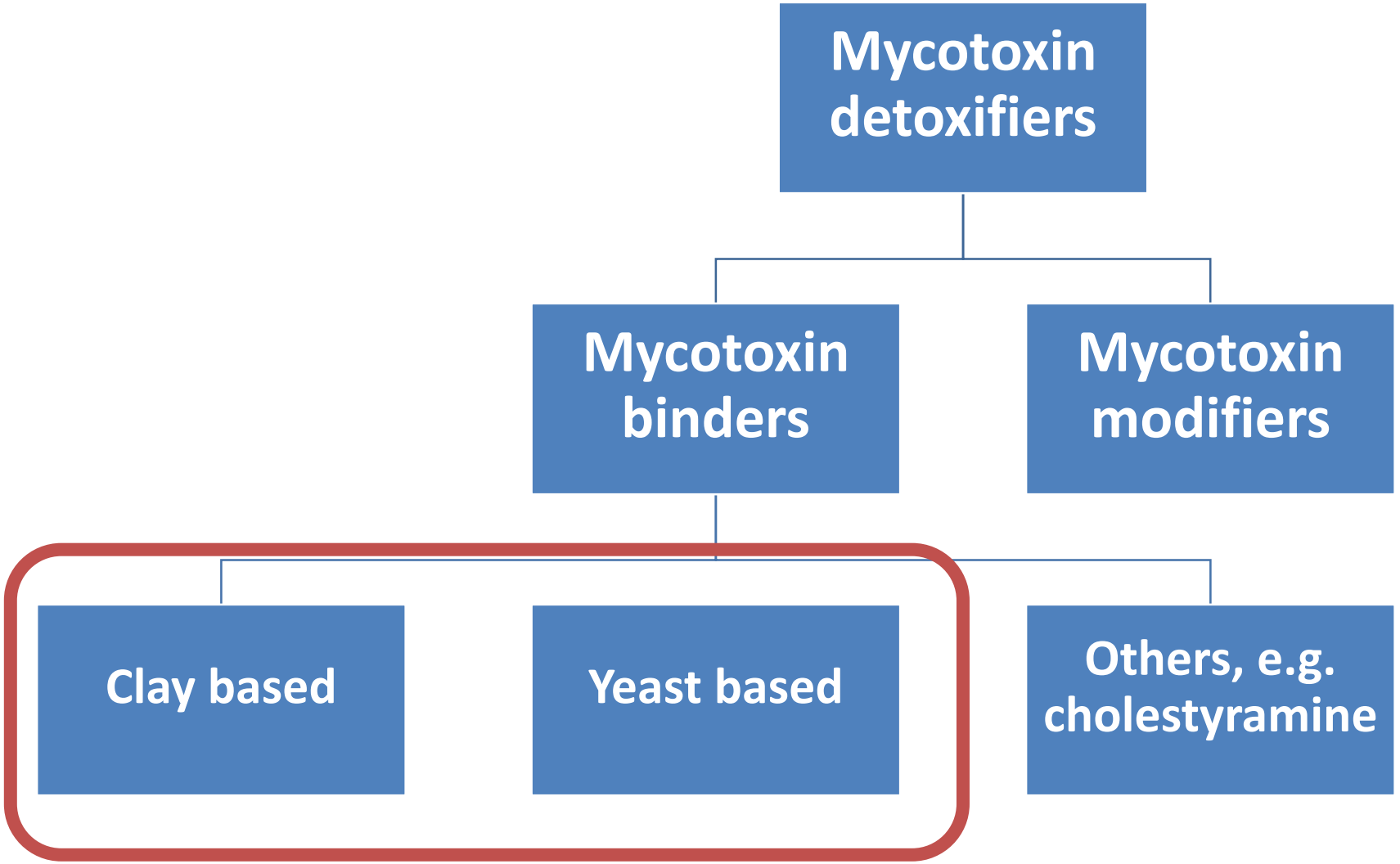
MYTOX

www.mytox.be

38th Mycotoxin Workshop, May 2-4, 2016, Berlin

# Introduction: Mycotoxin binders



# Introduction: Mycotoxin binders

- Feed additive: as mycotoxin binder

  Recommended level: 1 – 2 g/kg (0.1% - 0.2%)

**COMMISSION REGULATION (EC) No 386/2009**

**of 12 May 2009**

**amending Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the establishment of a new functional group of feed additives**

**(Text with EEA relevance)**

- Feed additive: for technological purposes

  Maximally 20 g bentonite/kg feed (2%)

**REGULATION (EC) No 1831/2003 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL**

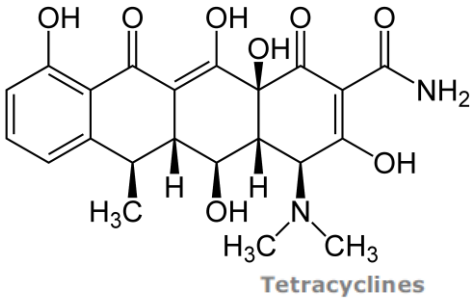
**of 22 September 2003**

**on additives for use in animal nutrition**

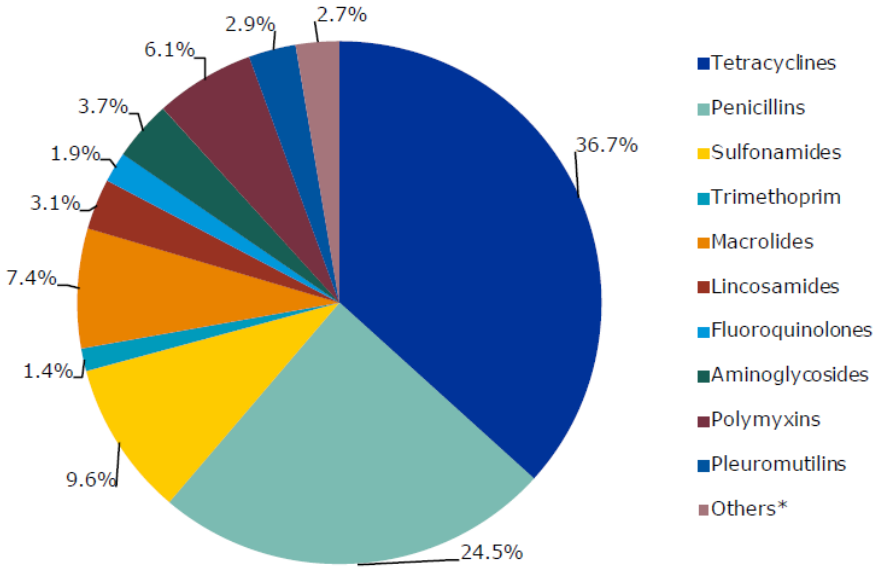
**(Text with EEA relevance)**

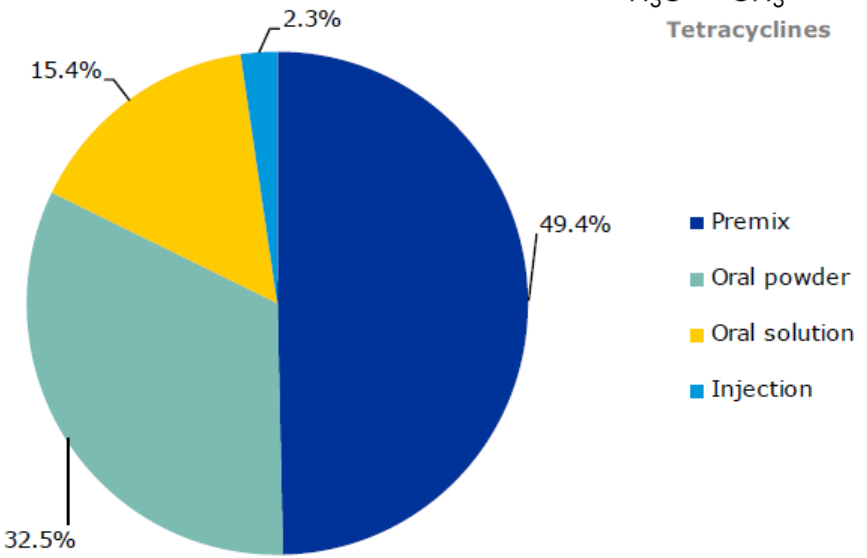
# Introduction: Doxycycline (DOX)

- Tetracycline antibiotic
- *Mycoplasma spp., Actinobacillus pleuropneumoniae, Bordetella bronchiseptica, etc.*
- Oral bioavailability is lower in fed animals



Tetracyclines




(ESVAC, 2016)

# Aims

Mycotoxin binders: feed additives

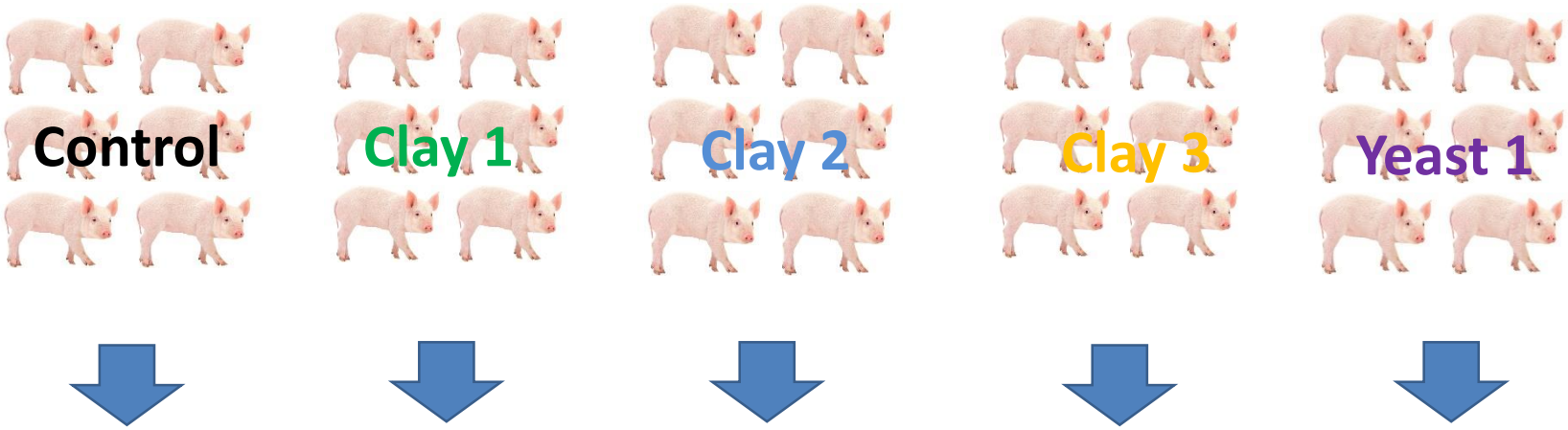
Antimicrobials (doxycycline):
Oral administration *via* feed/drinking water

Non-specific interaction in the GIT?

Interaction depends on
- inclusion rate?
- prandial status?

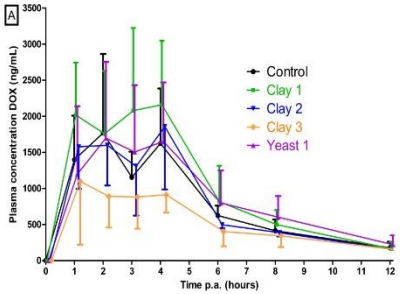
# Experiment 1: Study design

**Fasted** animals, single oral bolus:
- Daily dosis of mycotoxin binder (~**0.2% inclusion rate**)
- DOX (10 mg/kg BW)




Blood sampling at different time points after DOX administration
LC-MS/MS analysis of DOX in plasma
Comparing PK

# Experiment 1: Results

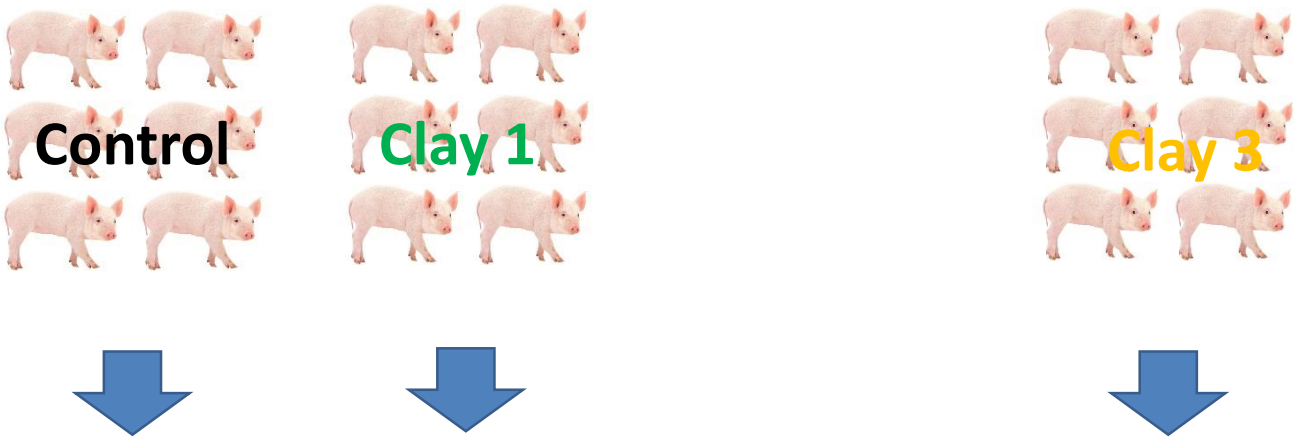



$$Relative\ F(\%) = \frac{AUC\ test\ group}{AUC\ control}\ x\ 100$$

| Treatment group | Control | Clay 1 | Clay 2 | Clay 3 | Yeast 1 |
|---|---|---|---|---|---|
| $AUC_{0\text{-}12h}$ (h·µg/mL) | 9.60 ± 3.49 | 12.29 ± 4.57 | 9.73 ± 2.35 | 6.37 ± 2.63 | 10.72 ± 5.59 |
| $AUC_{0\text{-}inf}$ (h·µg/mL) | 10.56 ± 3.97 | 12.90 ± 4.84 | 10.43 ± 2.42 | 7.54 ± 2.67 | 11.78 ± 6.04 |
| Relative F (%) | 100.00 ± 37.61 | 122.31 ± 45.87 | 98.91 ± 22.95 | 71.50 ± 25.34 | 111.69 ± 57.28 |
| $T_{max}$ (h) | 2.00 ± 1.10 | 2.83 ± 1.47 | 2.50 ± 1.64 | 2.17 ± 1.47 | 2.50 ± 1.22 |
| $C_{max}$ (µg/mL) | 2.01 ± 0.91 | 2.46 ± 0.90 | 2.12 ± 0.77 | 1.31 ± 0.75 | 1.93 ± 1.06 |
| $k_{el}$ (1/h) | 0.23 ± 0.08 | 0.29 ± 0.05 | 0.22 ± 0.04 | 0.21 ± 0.13 | 0.23 ± 0.06 |
| $T_{1/2el}$ (h) | 4.83 ± 1.74 | 3.57 ± 0.52 | 4.69 ± 0.87 | 6.59 ± 3.95 | 4.60 ± 1.11 |
| Vd/F (L/kg) | 4.77 ± 1.35 | 3.07 ± 1.12 | 4.66 ± 1.14 | 9.26 ± 5.81 | 5.36 ± 3.92 |
| Cl/F (L/h/kg) | 1.09 ± 0.46 | 0.88 ± 0.33 | 1.00 ± 0.23 | 1.45 ± 0.43 | 1.15 ± 0.76 |

# Experiment 2: Study design

**Fasted** animals, single oral bolus:
- Daily dosis of mycotoxin binder (~**1% inclusion rate**)
- DOX (10 mg/kg BW)

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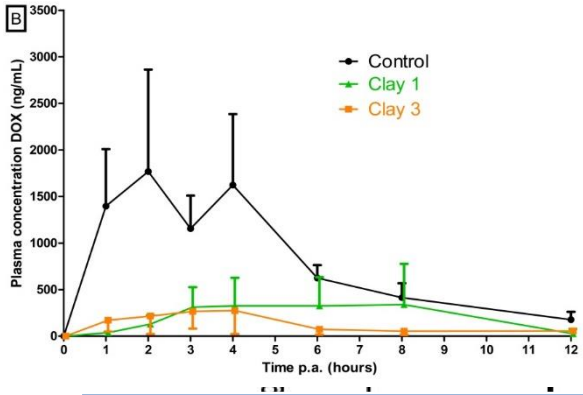
# Experiment 2: Results

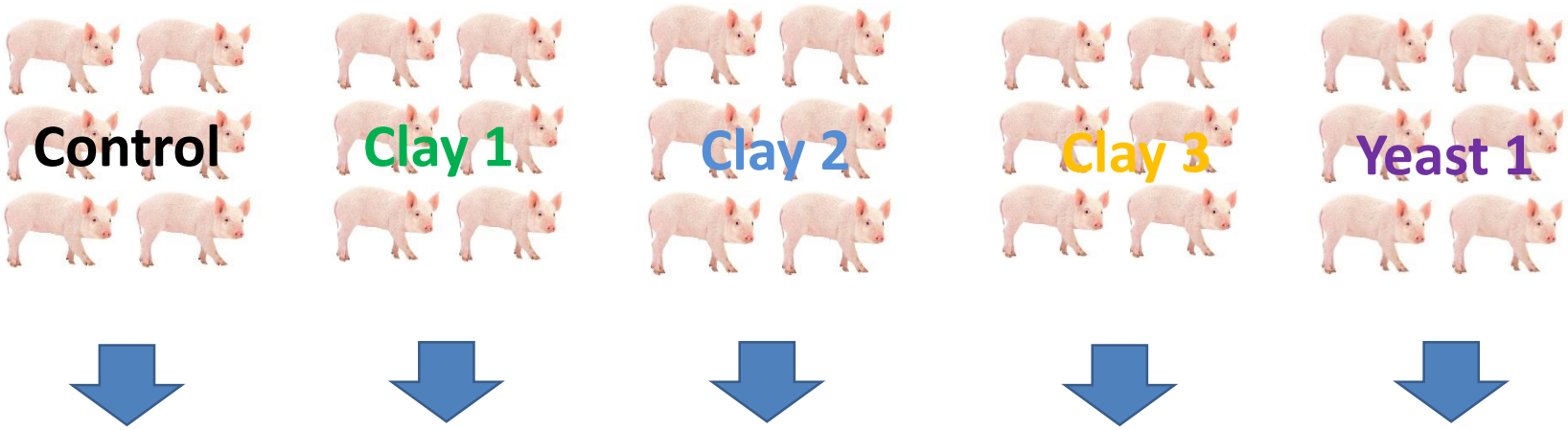



Control
Clay 1

| Treatment group | Control | Clay 1 | Clay 3 |
|---|---|---|---|
| $AUC_{0\text{-}12h}$ (h·µg/mL) | 9.60 ± 3.49 | 2.26 ± 2.16* | 1.49 ± 0.94† |
| $AUC_{0\text{-}inf}$ (h·µg/mL) | 10.56 ± 3.97 | 2.28 ± 2.55* | 2.07 ± 1.02* |
| Relative F (%) | 100.00 ± 37.61 | 21.62 ± 24.14* | 19.67 ± 9.64* |
| $T_{max}$ (h) | 2.00 ± 1.10 | 4.50 ± 2.07 | 4.50 ± 3.83 |
| $C_{max}$ (µg/mL) | 2.01 ± 0.91 | 0.45 ± 0.40* | 0.32 ± 0.21* |
| $k_{el}$ (1/h) | 0.23 ± 0.08 | 0.33 ± 0.16 | 0.15 ± 0.06 |
| $T_{1/2el}$ (h) | 4.83 ± 1.74 | 3.44 ± 1.19 | 7.44 ± 2.44 |
| Vd/F (L/kg) | 4.77 ± 1.35 | 26.77 ± 18.28 | 45.46 ± 32.81‡ |
| Cl/F (L/h/kg) | 1.09 ± 0.46 | 8.16 ± 4.80‡ | 6.11 ± 3.51‡ |

# Experiment 3: Study design

**Continuous administration in the feed**:
- Mycotoxin binder (**0.2% inclusion rate**)
- DOX: 270 mg/kg feed (~10 mg/kg BW)

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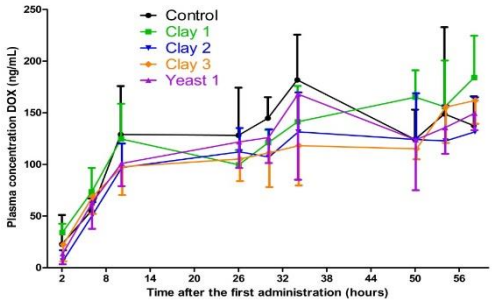
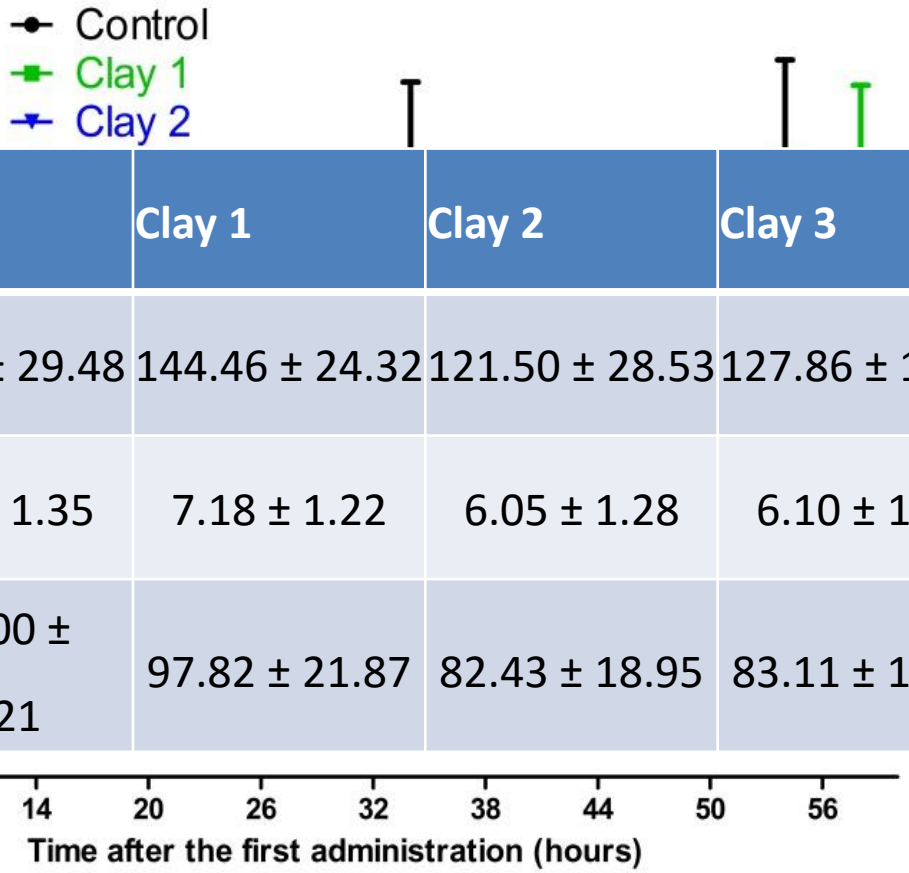
# Experiment 3: Results




| Treatment | Control | Clay 1 | Clay 2 | Clay 3 | Yeast 1 |
|---|---|---|---|---|---|
| $C_{ss}$ (ng/mL) | 143.02± 29.48 | 144.46 ± 24.32 | 121.50 ± 28.53 | 127.86 ± 15.89 | 137.23 ± 27.37 |
| $AUC_{0\text{-}58h}$ (h·µg/mL) | 7.34 ± 1.35 | 7.18 ± 1.22 | 6.05 ± 1.28 | 6.10 ± 1.04 | 6.76 ± 1.60 |
| Relative F (%) | 100.00 ± 24.21 | 97.82 ± 21.87 | 82.43 ± 18.95 | 83.11 ± 14.54 | 92.10 ± 13.28 |

# Discussion & Conclusions

- Interaction possible at high dose, in fasted animals
- No interactions observed at low dose
- Confirms *in vitro* results using feed containing buffered matrix (Poster 17)
- Bolus mo
- EFSA (201
  - Highe
  - Steady roduct in feed, 5 days s
- Further ir

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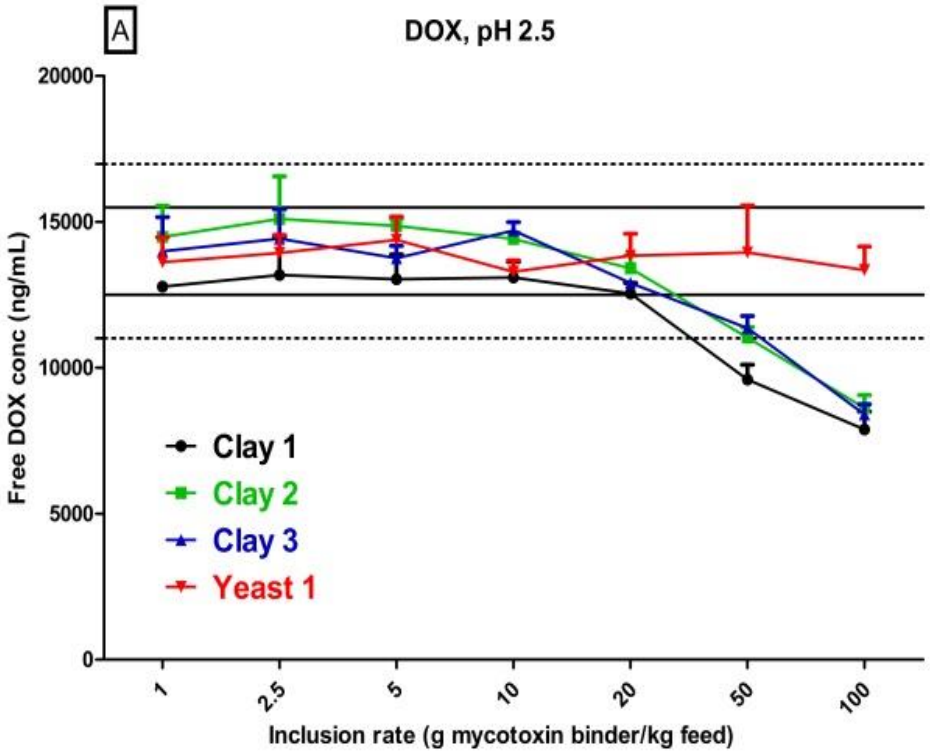


EFSA Journal 2010; 8(7):1693

NTIFIC OPINION

of guidelines for the assessment of additives
ances for reduction of the contamination of
by mycotoxins'[1]

ts or Substances used in Animal Feed (FEEDAP)[2,3]

European Food Safety Authority (EFSA), Parma, Italy



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# Acknowledgements

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federal public service
HEALTH, FOOD CHAIN SAFETY AND ENVIRONMENT